Remarks

In view of the above amendments and the following remarks, favorable reconsideration of the outstanding office action is respectfully requested.

Claims 1-32 and 51 remain in this application. Claims 1 and 51 have been amended. Claims 33-50 have been canceled. New claims 52 and 53 have been added. Support for the claim amendment can be found in paragraph 0032, and support for the new claims can be found in paragraph 0004. Typographical errors in the specification have been corrected. A page entitled "Marked-Up Specification and Claims to Show Changes Made" is attached.

1. Drawings

The Examiner stated that a petition is required under 37 C.F.R. 1.84(a)(2) to accept color photographs, accompanied by the fee set forth in 37 C.F.R. 1.17(h). Applicants also enclose a petition under 37 CFR 1.84 (a)(2), the appropriate fee, three sets of color drawings, and a black and white photocopy of the drawings. The specification has been amended to include a statement indicating that color drawings are contained in the patent.

The drawings were objected to because the margins were not acceptable on Figure 3. Applicants submit a replacement sheet for Figure 3 in an enclosed Letter to the Official Draftsperson.

2. § 112 Rejections

Claims 1-32 and 51 were rejected under the first paragraph of 35 U.S.C. § 112, the Examiner asserting that "the specification does not clearly and adequately describe the invention and therefore the scope of the invention would encompass the prior art." After stating that various components of the invention are known in the prior art, the Examiner states that "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." The Examiner asks the question, "where is the point of novelty in the invention?"

Applicants respectfully traverse these rejections. MPEP Section 2164.01 states that the test of enablement is whether a person skilled in the art upon reading the specification "can make and use the invention without undue experimentation." Applicants respectfully submit the specification is replete with information to enable a skilled artisan to make and use the invention without undue experimentation. Claim 1 is directed to an array comprised of a plurality of membrane microspots stably associated with a surface of a substrate. Claims 2-32 depend from claim 1. Claim 51 is directed to a an array comprising a plurality of biological membrane microspots stably associated with a surface of a glass substrate, wherein

the surface is coated with γ-aminopropyl-silane and the biological membrane microspots comprise a G-protein coupled receptor. Multiple examples of methods and apparatus for making and using the claimed arrays are contained in the detailed description of the invention. The arrays are described on pages 8-10, substrates that can be used to form the arrays are described on pages 10-11, coating materials to enable production of the arrays are disclosed on pages 11-13, biological membranes are described on pages 13- 14, and proteins, including G-protein coupled receptors, are described on pages 14-15. Methods and apparatus for preparation and use of the arrays are disclosed on pages 15-18, and working examples are provided on pages 18-15. All of the information listed above provides various methods and apparatus that would enable one skilled in the art to make and use the claimed invention. Accordingly, applicants respectfully request withdrawal of the rejection.

The point of novelty of the invention is not pertinent to the analysis under section 112, first paragraph. As discussed above, the specification clearly provides ample information to enable a skilled artisan to make and use the invention. The novelty of the invention will be addressed below with respect to section 102 rejections.

The Examiner also rejected claims 1-32 and 51 under the second paragraph of 35 U.S.C. § 112, stating that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In making this rejection, the Examiner states that the term "biological membrane" is vague and confusing because the "biological membrane" as defined by the specification incorporates both synthetics such as liposomes and vesicles and naturally occurring membranes (pg. 13, lines 26-31). The Examiner states that based on a conventional definition of the "biological membrane", a biological membrane is a membrane with a biological component such as specific binding. Applicants respectfully traverse this rejection.

MPEP Section 2173.04 states that "[i]f the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph." Applicants respectfully submit that claims 1-32 and 51 set out and circumscribe with a reasonable degree of particularity the particular areas the inventors regard as their invention. It is well known in the art that biological membranes can be membranes that are naturally occurring and synthetically produced. On page 13, paragraph 50, the specification provides a definition that is consistent with this well-known fact. Applicants respectfully disagree with the Examiner's "conventional definition" of a biological membrane and respectfully request an affidavit from the Examiner under 37 C.F.R.

1.104(d) to support this definition. Even assuming that this definition is correct, which is denied, applicants respectfully submit that synthetic membranes can include a biological component, for example, but not limited to specific binding. Synthetic glycolipids are just one of many examples of synthetic proteins that contain a biological component. Synthetic glycolipids are lipids with a sugar moiety in their headgroups that are targets for a number of biomolecules such as proteins or organelles such as bacteria or virus. Hundreds of synthetic glycolipids with biological components are available from Sigma or Avanti Lipids. Applicants respectfully request withdrawal of the rejection.

3. § 102 Rejections

The Examiner rejected claims 1-3, 6-9, 11-14, 20-21 and 27-32 under 35 U.S.C. § 102(b) as being anticipated by Bieri et al. (*Nature Biotechnology*, **1999**, 17(11):1105-1108). The Examiner asserts that Bieri teaches a patterned self assembled membrane bound sensor chip. The Examiner states that the sensor is comprised of a gold surface, a membrane layer that is bound to the surface through a biotinylated thiols, and G protein coupled receptors are incorporated in the membrane.

Applicants respectfully traverse this rejection. To anticipate a claim, a reference must teach every limitation in the claim. Applicants' invention, as defined by claims 1-32 and 51, are directed to arrays of biological membrane microspots that are stably associated with a surface of a substrate. New claims 52 and 53 are directed to arrays of biological membrane microspots on a substrate that are capable of being produced, used, or stored in an environment exposed to air under ambient humidity. The Bieri article fails to teach or suggest an array of microspots on the surface of a substrate. According to the present invention, arrays comprised of a plurality of microspots enable the formation of high density arrays of membranes and high throughput screening of microarray based assays. The Bieri article discloses an array comprised of stripes of membranes on a substrate, not microspots.

In addition to the failure to disclose an array of comprising a plurality of biological membrane microspots on a substrate, the Bieri article fails to teach or suggest arrays of membranes that are stably associated with the surface of the substrate or arrays that are capable of being produced, stored or used in an environment exposed to air under ambient humidity. A definition of stably associated on pages 8-9, paragraph 32 of the specification means that the membrane remains adsorbed when drawn through an air-water interface. Applicants' specification at paragraph 003 describes several methods for preparing arrays of membranes that involve fabricating grids or patterns on the surface of a substrate and that require the membrane patterns to be printed on surfaces immersed under water. These

patterned membranes were not stably associated with the substrate because they desorbed when drawn through an air-water interface. Printing arrays underwater limits the ability to produce arrays of biological membrane microspots because many devices for printing microspots are not adapted to print underwater.

Applicants respectfully submit that the Bieri reference cited by the Examiner fails to teach or suggest an array of membrane microspots stably associated with the surface of the substrate, and more specifically membrane microspots that would not spontaneously desorb when drawn through an air-water interface. Furthermore, Bieri fails to teach arrays that are capable of being produced, stored or used in an environment exposed to air under ambient humidity. The Bieri article discusses performing assays using surface plasmon resonance (SPR) in a flowthrough assay format, meaning the membrane sample remains immersed in a liquid (see page 1107, column 2, second full paragraph of the Bieri article). The Experimental protocol section of the Bieri article makes clear that the membrane patterns (which are striped patterns, not microspots) were processed in cuvettes diluted in buffer solution (see page 1108, first column, third full paragraph). Bieri states that measurements were performed in a stirred cuvette, again making clear that the membrane patterns were only stable if they were kept in solution (see page 1108, first column, fourth full paragraph). The Bieri article fails to teach an array of membrane microspots that do not desorb from the substrate when drawn through an air-water interface because the substrates remain immersed in a solution during formation of the striped patterns and measurement. Accordingly, applicants respectfully submit that the Bieri article does not anticipate applicants' claims 1-32 and 51, and request withdrawal of the rejection.

The Examiner rejected claims 1-6, 8-9, 11-14, 20-21, 27-32 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,756,355 (the Lang '355 patent). Applicants respectfully traverse this rejection.

The Lang '355 patent fails to teach or suggest every limitation recited in claims 1-6, 8-9, 11-14, 20-21, 27-32. Lang discloses a bilayer lipid membrane sensor including a gold surface, a first lipid layer and a second lipid layer. The Lang '355 patent discloses bulk layers of first lipid layers and second lipid layers. Arrays of biological membrane microspots are not disclosed or suggested in the Lang '355 patent. In addition, column 4, lines 48-50 of the Lang '355 patent states that preferably, the sensor is constructed in the form of a small compartment for retention of an aqueous medium above the second layer. This indicates that the second lipid layer must remain immersed to maintain stability. There is absolutely no teaching or suggestion in the Lang '355 patent of an array of biological

membrane microspots stably associated with a surface of a substrate. Additionally, there is no teaching or suggestion in the Lang '355 patent of arrays that are capable of being produced, stored or used in an environment exposed to air under ambient humidity. Accordingly, applicants respectfully request withdrawal of the rejection.

4. § 103 Rejections

The Examiner rejected claims 7, 10, 15-19, 26 and 32 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,756,355 (the Lang '355 patent) in view of U.S. Patent No. 4,933,285 (the Patton '285 patent). The Examiner states that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to include in the biological membrane bound sensor of Lang '355 the plastic or glass substrate and coating material such as gamma-aminopropylsilane as taught by the Patton '285 patent because the polymeric linkage would provide enhanced stabilities of the immobilized biomolecules and the choice of substrate such as plastic or glass would provide the advantage of economy and convenience. The Examiner further states that the features of remaining dependent claims are either specifically described by the reference (e.g. glass or silane compound), or constitute obvious variations in parameters which are routinely modified in the art (e.g. contact angle), and which have not been described as critical to the practice of the invention. Applicants respectfully traverse these rejections.

To establish a prima facie case of obviousness, the Examiner must meet three basic criteria. There must be some suggestion or motivation from the references themselves or the knowledge generally available to one of ordinary skill in the art to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be in the prior art, and not on the applicants' disclosure. MPEP Section 2142. In addition, in determining the differences between the prior art and the claims, the question is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. MPEP Section 2141.02. Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness.

First, the deficiencies noted above in the Lang '355 patent are not remedied by the teachings of the Patton '285 patent. The Lang '355 patent and the Patton '285 patent fail to disclose or suggest, alone or in combination, arrays of membrane microspots stably associated with the surface of a substrate or arrays that are capable of being produced, stored or used in an environment exposed to air under ambient humidity. As discussed above, the

Lang '355 patent teaches bulk layers and not an array comprising a plurality of membrane microspots. In addition, the bulk layers in the Lang '355 patent must be immersed in a small compartment to retain an aqueous medium above the outermost layer. The Patton '285 patent discloses a process for building multiple bulk monolayers of polymer linkages on a surface of a solid phase, not arrays comprising a plurality of membrane microspots. There is no teaching or suggestion in the Patton '285 patent of arrays of membrane microspots stably associated with the surface of a substrate or arrays that are capable of being produced, stored or used in an environment exposed to air under ambient humidity. Accordingly, applicants respectfully request withdrawal of these rejections.

The Examiner rejected claims 22-25 under 35 U.S.C. § 103(a) as being unpatentable over the Lang '355 patent in view of Plant (*Langmuir*, **1999**, 15(15):5128-5135) (the Plant article). Applicants traverse this rejection.

As discussed above, Lang '355 fails to disclose or suggest an array of biological membrane microspots on the surface of the substrate or arrays that are capable of being produced, stored or used in an environment exposed to air under ambient humidity. In addition, the Lang '355 bulk layer membranes are not stably associated with the surface of a substrate. The Plant article is cited in the background section of applicants' specification. There is no teaching or suggestion in the Plant article of an array of biological membrane microspots, or membranes that are stably associated with the surface of a substrate. Both the Lang '355 patent and the Plant article disclose the formation of bulk layers of membranes, not formation of arrays of microspots of membranes. In addition, as discussed above, the Lang '355 patent requires the second layer to be immersed in water. There is no teaching or suggestion of arrays of membrane microspots stably associated with the surface of a substrate in the Lang '355 patent or the Plant article alone or in combination. Accordingly, applicants respectfully request withdrawal of the rejection.

5. Conclusion

In view of the foregoing remarks, the application is believed to be in condition for allowance, and early notice to this effect is earnestly solicited. If allowance of this application may be expedited by resolution of simple issues through a telephone conference, the Examiner is welcome to call the undersigned.

Applicant believes that no extension of time is necessary to make this Amendment timely. Should Applicant be in error, Applicant respectfully requests that the Office grant such time extension pursuant to 37 C.F.R. § 1.136(a) as necessary to make this Amendment timely, and hereby authorizes the Office to charge any necessary fee or surcharge with

respect to said time extension to the deposit account of the undersigned attorney, Deposit Account 50-2056.

Respectfully submitted,

Date: 11/25/2002

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8:
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November 25, 2002
Date of Deposit

Scott S. Servilla
Name of applicant, assignee, or Registered Representative

Signature

November 25, 2002
Date of Signature

MARKED-UP SPECIFICATION AND CLAIMS TO SHOW CHANGES MADE

SPECIFICATION:

Originally numbered Paragraph 0053 under the Heading "Preparation of the Arrays"

[0053] The arrays of the present invention are prepared using [micropaterning] micropatterning techniques. Such techniques are well known in the art. In a preferred method of preparation, the tip of a probe (also referred to as a "pin") is immersed into a solution of biological membrane. The tip is removed from the solution to provide solution adhered to the tip. The lipid solution is contacted with the surface of a substrate to thereby transfer the solution from the tip to the surface.

Originally numbered paragraph 0074 under the Heading "Fabrication and Storage of GPCR Arrays":

[0074] Arrays of GPCRs were fabricated by conventional robotic pin printing, using a quill-pin printer as described in the Experimental Section. Boxer and co-workers have described the importance of transferring membranes onto the solid-support under water; we were, however, concerned that the lipid solution wetted onto the pin would partially dissociate from the pin under water and cause cross-contamination during printing. Moreover, slide racks in commercially available printers are not set up for printing under water. The ability to use [of-the-shelf] off-the-shelf printing equipment for fabricating membrane-protein arrays is an important step towards the widespread fabrication and development of these arrays for bioanalytical applications.

CLAIMS:

1. (Amended) An array comprising a plurality of biological membrane microspots stably associated with a surface of a substrate.

51. (Amended) An array comprising a plurality of biological membrane microspots stably associated with a surface of a glass substrate, wherein the surface is coated with γ-aminopropyl-silane and the biological membrane microspots comprise a G-protein coupled receptor.